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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,866	05/29/2001	Brian Sorrentino	02427/1203347-US2	4688

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,866	SORRENTINO ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,22-24 and 29-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16, 22-24, 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and Remarks submitted 12/20/2005 have been entered. Claim 16 has been amended, claims 17, 21, 25-28 have been canceled, and claims 29-32 are newly submitted. Claims 16, 22-24, 29-32 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 12/20/05 response would be addressed to the extent that they apply to current rejection.

Information Disclosure Statement

The information disclosure statement filed 12/20/2005 fails to comply with 37 CFR 1.97(c) because it lacks a complete statement as specified in 37 CFR 1.97(e). It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In view of the recent decisions in Noelle v. Lederman, 355 F.3d 1343 (Fed. Cir. 2004) and SmithKline Beecham Corporation v. Apotex Corp., 403 F.3d 1328 (Fed. Cir.

2005), the previous written description and enablement rejections under 35 USC 112, first paragraph, have been withdrawn.

Claim Objections

Claims 16, 22-24, 29-32 are objected to for failing to further limit the claimed subject matter.

The claims are directed to isolated antibodies that bind to an extracellular portion of a BCPR protein. Claims recite, "wherein the antibody fails to bind to living MCF-7 cells that do not express BCRP" or alike. These phrases do not appear to further describe a functional characteristic of the antibody, since an antibody specifically binds to a protein would not do so when the protein is absent.

Further, applicant points to the support in paragraph 0074-0077 of the specification for the newly added phrase. It is noted, this portion of the specification provides a method outlined in figure 1 of the specification, where the screening of antibody-secreting hybridoma includes a step to eliminate hybridoma clones secreting antibodies that non-specifically bind to MCF7 cells but not to BCRP. It is noted this step is to remove those clones that do not secret a BCRP-specific antibody but antibodies cross-react with surface antigens on MCF7 cells. Thus, this step does not appear to add any structural or functional limitation on the claimed antibody itself, it only describes the process for selecting hybridoma cell clones.

Appropriate correction or clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16, 22-24 stand rejected and the rejection applies to claims 29-32 under 35 U.S.C. 103(a) as being unpatentable over *Ross et al* (US 6,313,277, IDS/AA), in view of *Mechetner et al* (US 5,994,088), for reasons of record and following.

The amended claim 16 adds a phrase describing the binding specificity of the claimed antibody, which is the intrinsic property of the antibody produced by the combined teachings of the cited references. New claims 31 and 32 are product-by-process claims, which has been taught by the combined teachings as discussed in details in the previous Office actions. Claim 30 is drawn to an immuno-detection kit comprising the claimed antibody, which is a well-known means for using the claimed antibody in commerce.

In the Remark filed 12/20/05, Applicant acknowledges that Ross describes the human BCRP amino acid and its corresponding cDNA, contemplates preparing polyclonal antibody, and asserts that the only mention of monoclonal antibodies in Ross is a general statement and citing to the general methods for making antibodies of Kohler et al.

The argument has been fully considered but found not persuasive. As an initial matter, it is noted that claims encompasses both polyclonal and monoclonal antibodies.

The argument has been found not persuasive because *Ross et al* disclose fully characterized antigen BCRP and various methods known in the art that could be used to make either polyclonal or monoclonal antibodies, such as immunizing a mammal with a BCRP protein (paragraph bridging columns 1 & 2) or immunizing a mammal with a whole cell with the antigen of interest on its surface and subsequently producing hybridoma secreting such antibody with spleen cells of the immunized mice as taught by *Kohler et al,* (column 4, line 50-57). *Ross et al* do not particularly mention making the antibody with a living cell that expresses the extracellular epitope in its natural conformation, but *Mechaetner et al* supplemented the deficiency by illustrating production of an antibody that binds to P-glycoprotein (Pgp) antigen expressed on living cells in its natural conformation, which Pgp antigen belongs to the same family of proteins as instant BCRP, i.e. ABC transporter protein (e.g. abstract, claims 1-9). *Mechaetner et al* teach that several of such antibodies recognizing the extracellular portion of the Pgp are known in the art, such as the 4E3 mAb as taught by *Arcesi et al* that does not disrupt drug efflux, and UIC2 that inhibit Pgp-mediated drug efflux (column 4, lines 30-65 and column 6, lines 19-46), wherein they clearly teach that the UIC2 recognizes the extracellular portion of the Pgp in its biochemical conformation (natural conformation). They go on to teach that antibodies reacting to the extracellular epitopes of Pgp are more useful for diagnosis and treatment (column 3, lines 61-67). They go on to teach the method of making such antibody, i.e. transfecting balb/c 3T3 fibroblasts with a vector expressing the cDNA of Pgp (MDR1 gene), immunizing syngeneic mice with selected cells expressing high levels of Pgp, and producing hybridomas using

spleen cells of the immunized mice and selecting for antibodies of interest (e.g. column 12, lines 1-37). They also teach that the method could be used for producing monoclonal or polyclonal, chimeric or humanized antibodies (column 11, lines 45-55).

Applicants argue that Mechetner is silent regarding BCRP proteins, BCPR conformations, and BCRP antibodies.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, *Mechetner* is relied on showing that it was well known in the art to produce an antibody that binds to an antigen in its natural conformation, and the method of obtaining such. *Mechetner et al* use the 3T3 cells expressing Pgp, and teach, "THE PARTICULAR SCREENING METHOD USED WAS NOT CRITICAL PROVIDED THAT IT WAS CAPABLE OF DETECTING ANTI-HUMAN MDRI PGP MAB. IT IS IMPORTANT, HOWEVER, THAT CELLS ARE NOT PENNEABILIZED AND FIXED DURING SCREENING (I.E. THEY ARE LIVING CELLS), SO THAT ONLY ANTIBODIES REACTIVE WITH EXTRACELLULAR PROTEIN DOMAINS ARE DETECTED" (column 12, lines 37-51, emphasis added). *Mechetner et al* clearly suggest to make an antibody reactive with extracellular protein domains via expressing such in a living cell.

Moreover, *Ross et al* disclose the BCRP-transfected MCF-7 cells, and using such for assaying BCRP-targeted drug interaction (fig. 4D). Thus, it flows logically that one of skilled in the art intending to make a BCRP specific antibody that binds to the extracellular protein epitope in its natural conformation would use the BCRP-expressing

MCF-7 cells as taught by *Ross et al* for antibody production and screening as taught by *Mechetner et al*.

In response to applicant's argument that *Mechetner* is silent regarding BCRP, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, in light of the teachings of the *Ross et al* in view of *Mechetner* and the state of the art in making antibodies as a whole, it would have suggested to one of ordinary skill in the art at the time the invention was made to employ the method as taught by *Mechaetner et al* in making an antibody that binds to the extracellular epitope of BCRP in its natural conformation, wherein the antibody would intrinsically binds to living MCF-7 or 3T3 cells expressing BCRP on their surface since that *Mechetner et al* use 3T3 cells as transfected antigen-expressing cell and *Ross et al* teach BCRP-transfected MCF-7 cells. Given the methods of making and screening for antibodies that binds to an extracelluarl portion of the ABC transporter protein is known in the art, given the knowledge regarding the importance of the extracellular portion of an ABC transporter protein, and given the cDNA of BCRP and transfected MCF-7 cells provided by *Ross et al*, it is within the knowledge of the skilled to make a similar antibody as 4E3 or UIC2 that binds to the extracellular epitope of BCRP in its natural conformation. Additionally, the court has determined that finding obviousness does not require

expressly written motivation to combine in prior art since the motivation to combine may be found in the nature of the problem to be solved (*Ruiz v. A.B. Chance Co.*, 69 USPQ2d 1686 CA FC 2004).

This position of the Office is further supported by the recent decisions of the court, who states, "IF APPLICANT HAS DISCLOSED FULLY CHARACTERIZED ANTIGEN, EITHER BY STRUCTURE, FORMULA, CHEMICAL NAME, OR PHYSICAL PROPERTIES, OR BY DEPOSITING PROTEIN IN PUBLIC DEPOSITORY, THEN APPLICANT CAN CLAIM ANIBODY BY ITS BINDING AFFINITY TO THAT DESCRIBED ANTIGEN" Noelle v. Lederman, 355 F.3d 1343 (Fed. Cir. 2004) Here, *Ross et al* disclosed a fully characterized antigen by its structure, and *Mechetner et al* taught the method of making and the necessity of producing an antibody that recognizes an ABC transporter in its natural conformation in a living cell. Thus, following these teachings and by routine experimentation, the skilled artisan would have had a reasonable expectation of success producing an antibody that recognizes extracellular portion of a BCRP in its natural conformation.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, *Ross et al* have explicitly suggested using art known methods for producing antibodies specific to BCRP

protein, and *Mechetner et al* explicitly teach the desirability and method for producing an antibody that binds extrocellular portion of an antigen on a living cell. Thus the suggestion and motivation are clearly taught.

Applicants then pointed to an antibody 5D3 disclosed in a post-filing date publication by *Ozvegy-Laczka et al* which compared 5D3 to antibodies BXP-21 and BXP-34, each fails to recognizes ABCG-2 on a living cell or recognizes extracellular portion of the BCRP in its natural conformation.

In response, it is noted that BXP-21 was generated against an N-termal intracellular epitope (page 10 of the *Ozvegy-Laczka et al*), and BXP-34 was generated using sonicated MCF-7 cells, thus it would not be a surprise that they fail to recognize the extracellular epitope of the BCRP. Since these antibodies are produced with a different method, its failure of recognizing extracellular portion of the BCRP of these antibodies do not support the argument that using the method taught by *Mechetner et al* would fail to produce antibodies with instantly claimed characteristics.

Applicant go on to assert that prior to the inventors' disclosure, no one had successfully reported the production of antibodies that would bind specifically to a native human or murine BCRP conformation expressed on living cells. The prevailing sentiment by those skilled in the art was that such techniques would NOT work citing Sarkadi declaration as support.

Concerning the prevailing sentiment in the art, at the time of submission of *Sarkadi* declaration, Applicant also submitted a declaration by *Dr. Sorrentino*, who stated, "HAVING DEFINITELY GENERATED MORE THAN ONE ANTIBODY THAT RECOGNIZES AN

EXTRACELLULAR PORTION OF BCRP IN ITS NATURAL CONFORMATION ON LIVING CELLS, THIS METHOD IS CLEARLY A VALIDATED METHOD FOR GENERATING AN ANTIBODY TO AN EXTRACELLULAR PORTION OF THIS PARTICULAR ABC TRANSPORTER IN ITS NATURAL CONFORMATION. I EXPECT THAT THE ROBUSTNESS OF THIS METHOD WILL ALLOW FOR ROUTINE GENERATION OF ADDITIONAL ANTIBODIES OF THE TYPE CLAIMED BY SIMPLY REPEATING THE PROCEDURES DISCLOSED IN THE '586 AND '866 APPLICATIONS" (emphasis added). Apparently, the prevailing sentiment was not necessarily what *Dr. Sarkadi* stated, and nothing in the instant disclose appears to be contrary to expectations. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

As to the argument of lacking report of the claimed antibodies in the prior art publications, there may be many reasons to the fact, and obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

In conclusion, when considering the declarations along with the disclosure of the specification and the state of the art as a whole, it is noted the genus of the claimed antibody could be reasonably produced by the combined the teachings of *Ross et al* and *Mechetner et al*, and which rendered the claimed invention obvious. The statement of *Dr. Sorrentino* supports the conclusion of the instant rejection, i.e. following the combined teachings and routine experimentation, one would have had a reasonable expectation of success in generating antibodies of the claimed type. Accordingly, the rejection stands.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The fax numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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PRIMARY EXAMINER

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QJL
March 17, 2006